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10/590,927	04/09/2007	Axel Niendorf	5151-21PUS	4186

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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,927	NIENDORF ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-35 and 38-60* is/are pending in the application.

4a) Of the above claim(s) *29,30,33-35,42,43,46,48,52,53 and 55-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28,31,32,38-41,44-45,47,49-51,54,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed July 22, 2010. Claims 24-35 and 38-60 were previously pending, with claims 29, 30, 33-35, 42, 43, 46, 48, 52, 53 and 55-58 withdrawn from consideration. Applicants amended claims 24 and 25. Claims 24-28, 31, 32, 38-41, 44, 45, 47, 49-51, 54, 59 and 60 will be examined.

2. Applicants' amendments did not overcome any of the previously presented rejections for reasons given in the "Response to Arguments" below.

Response to Arguments

3. Applicant's arguments filed July 22, 2010 have been fully considered but they are not persuasive.

Regarding the rejection of claims 24-28, 31, 32, 38-41, 44, 45, 47, 49-51 and 54 under 35 U.S.C. 103(a) as being unpatentable over Adeyinka et al. and Sgroi et al., Applicants argue that their method is drawn to the use of at least four tissue sections, in which at least two sections which undergo non-morphological testing are sandwiched between two sections which undergo histological testing.

However, Applicants argue limitations which are not in the claims. The claims only require that at least one other portion is selected so that it is located between two portions used for histological testing. Therefore, the claims do not require at least four sections, they require at least three, one of which is used for molecular biology testing and the other two are outside of it. Therefore, since the tissue sections were from a single tumor, and consecutive sections were used for LCM and histological testing, at least one of the sections used for LCM was inherently between two sections used for histological testing.

The rejections are maintained.

Claim Interpretation

4. Applicants defined the term "non-morphological analytical testing" in paragraph [0017] as follows:

"In the discussion which follows, the term "nonmorphological analytical testing" is understood to mean especially molecular-biological analyses."

5. Applicants did not define the term "image processing system", therefore it is interpreted as any device or system used in visualizing samples or cells, such as a microscope, for example.

6. The phrase " wherein the determined at least one of a quantitative fraction of diseased tissue or cells and another morphological aspect is used as a reference quantity on which evaluation of a result of the non-morphological analytical testing is based" is interpreted as any correlation between morphological aspects and results of non-morphological analytical testing, since the term "reference quantity" was not defined.

7. The limitation "wherein in the histological/cytological examination, part of the tissue sample is used to quantify an amount of contaminating, non-diseased cells which are accounted for in the subsequent non-morphological analytical testing" is interpreted as using the quantity of non-diseased cells in any testing used subsequent to the histological/cytological analysis.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 24-28, 31, 32, 38-41, 44, 45, 47, 49-51 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adeyinka et al. (Clin. Cancer Res., vol. 8, pp. 3788-3795, 2002; cited in the previous office action) and Sgroi et al. (Cancer Res., vol. 59, pp. 5656-5661, 1999; cited in the previous office action).

A) Claims 24 and 25 will be considered together in claim 24, since it is a species of claim 25.

Regarding claims 24 and 25, Adeyinka et al. teach a method comprising:

preparing sections from the tissue sample (page 3789, second and third paragraph);

subjecting at least one portion of the sample to a histological/cytological examination (page 3789, third paragraph); and

subjecting at least another portion of the sample to a non-morphological analytical testing (page 3789, paragraphs 4 and 5; page 3790, paragraphs 2-4),

wherein in the histological/cytological examination, at least one of a quantitative fraction of diseased tissue or cells and another morphological aspect of the at least one portion of the sample is determined by an image processing system (page 3789, second paragraph; since the histological examination is performed using a microscope, as evidenced by Encyclopedia Britannica, Adeyinka et al. inherently teach using an image processing system),

wherein in the histological/cytological examination, part of the tissue sample is used to quantify an amount of contaminating, non-diseased cells which are accounted for in the subsequent non-morphological analytical testing (Adeyinka et al. teach adjusting the levels of mRNA expression by multiplying them by the percentage of ductal cells (page 3790, fifth and sixth paragraphs), and

wherein the determined at least one of a quantitative fraction of diseased tissue or cells and another morphological aspect is used as a reference quantity on which evaluation of a result of the non-morphological analytical testing is based (page 3791, paragraphs 2-4; Table 2; Fig. 2; page 3792, last paragraph; page 3793, paragraphs 1-3).

Regarding claim 26, Adeyinka et al. teach samples obtained by sectioning tissue blocks (page 3789, paragraphs 2-4). Since Applicants did not define "core sampler", any device used to section the tumor is considered to be a "core sampler".

Regarding claims 27 and 28, Adeyinka et al. teach that morphological appearance of the cells is correlated with the expression pattern of the genes (page 3791, paragraphs 2-4; Table 2; Fig. 2; page 3792, last paragraph; page 3793, paragraphs 1-3).

Regarding claims 31 and 32, Adeyinka et al. teach frozen samples (page 3789, second paragraph).

Regarding claims 38 and 39, Adeyinka et al. teach using the results for experimental pathological analysis (page 3791, paragraphs 2-4; Table 2; Fig. 2; page 3792, last paragraph; page 3793, paragraphs 1-3).

Regarding claims 40 and 41, Adeyinka et al. teach detecting biomolecules such as mRNA (page 3789, paragraphs 4 and 5; page 3790, paragraphs 2-4).

Regarding claims 44 and 45, Adeyinka et al. teach using microarrays (page 3790, second paragraph).

Regarding claims 47 and 49, Adeyinka et al. teach amplification (page 3790, third and fourth paragraphs).

Regarding claims 50 and 51, Adeyinka et al. teach staining (page 3789, second paragraph).

Regarding claim 54, Adeyinka et al. teach subjecting cells to additional histological examination (page 3789, third paragraph).

B) Regarding claims 24 and 25, Adeyinka et al. teach preparing the sections for non-morhological analysis from frozen tissue blocks which are mirror-images of formalin-fixed tissue blocks (page 3789, first paragraph), but do not teach using tissue sections adjacent to sections used for non-morphological testing for histological/cytological examination.

C) Sgroi et al. teach analysis of tissue sections from a breast cancer using histology and microarray hybridization (page 5656, paragraphs 3-5; page 5657, paragraphs 1-3). They teach confirmation of the array analysis data by analyzing sections adjacent to the ones used for microarray analysis by immunohistochemistry (page 5657, fifth paragraph; page 5659, last paragraph; page 5660, first paragraph). They also morphologically examined sections corresponding to the LCM sections used for PCR analysis (Fig. 3B).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the additional confirmation method of Sgroi et al. in the method of Adeyinka et al. The motivation to do so is provided by Sgroi et al., who state (page 5659, last paragraph; page 5660, first paragraph):

"As an additional means to confirm our data at the protein level, we performed immunohistochemical analysis of apolipoprotein using tissue sections that were adjacent to those

used for laser microdissection. Paralleling the differential expression pattern observed with the cDNA microarray and RTQ-PCR analysis, the invasive cells demonstrated abundant and strong immunoreactivity for apolipoprotein D, whereas the metastatic cells demonstrated rare and weak immunoreactivity (Fig. 3*B*). This result further supports the reliability of our expression data and demonstrates the cellular specificity of the apolipoprotein gene expression. Overall, the RTQ-PCR and immunohistochemistry results support the feasibility of our microarray experimental protocol as a means to assess *in vivo* transcript expression profiles."

11. Claims 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adeyinka et al. (Clin. Cancer Res., vol. 8, pp. 3788-3795, 2002; cited in the previous office action) and Sgroi et al. (Cancer Res., vol. 59, pp. 5656-5661, 1999; cited in the previous office action), as applied to claims 24 and 25 above, and further in view of Erlander et al. (US 2003/0186248 A1; cited in the IDS and in the previous office action).

Claims 59 and 60 are drawn to the methods of claims 24 and 25 used to adjust patient's individualized cancer therapy. Adeyinka et al. teach that products of genes identified using molecular analysis can serve as a basis for assessing the risk of progression of DCIS or providing targets for new therapies (page 3788, last sentence; page 3789, first paragraph).Erlander et al. teach that the results of correlation between histological/cytological features and sensitivity or resistance to a particular therapeutic agent or treatment, including information regarding the likelihood of success or failure of various treatment regimens for the disease (page 4, [0026]). Therefore, in view of these teachings of Adeyinka et al. and Erlander et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the information regarding treatment outcomes to adjust therapy of individual patients based on their histological and molecular signatures.

12. No claims are allowed.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
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September 8, 2010